Asymptomatic Hyperuricemia Treat or Not

By

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Uric acid day-Tanta 24/12/2015

Physiology

- Uric acid is a weak acid trioxypurine (M.W. 168) that is composed of a pyrimidine and imidazole substructure with oxygen molecules, which is produced primarily in the liver, muscle, and intestine.
- The immediate precursor of uric acid is xanthine, which is degraded into uric acid by xanthine oxido-reductase.
- Both exogenous (present in fatty meat, organ meats, and seafood) and endogenous purines are major sources of xanthine and uric acid in humans.
- Fructose, such as from added sugars and fruits, is another major source of uric acid.

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Contd.,

- Approximately two thirds of total body urate is produced endogenously, while the remaining one third is accounted for by dietary purines.
- The primary site of excretion of uric acid is the kidney. The normal urinary
- urate excretion in the range of 250 to 750 mg per day, approximately 70% of the daily urate production.

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Contd.,

- The classic paradigm of uric acid excretion consists of a four-step model with filtration, reabsorption, secretion, and postsecretory reabsorption; the latter three processes occur in PCT.
- More recently emphasis has focused on the role of specfic transporters, such as URAT1, SLC2A9, and others.
- The fractional urate excretion is only 8% to 10% due to reabsorption in PCT.
- Some adaptation occurs with renal disease, in which the fractional excretion of urate will increase to the 10% to 20%. The remainder of uric acid excretion occurs through the gut, where uric acid is degraded by uricolytic bacteria.
- The gastrointestinal tract may eliminate up to one-third of the daily uric acid load in the setting of CKD.

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Why should we treat?

- Acute HU nephropathy (TLS, mechanical obstruction of tubules)
- Uric acid nephrolithiasis (5-10% of renal stones, acidic urine)
- HU after renal Tx
- **Chronic gouty nephropathy**??????
- CV affliction
- Insulin resistance and DN
- HTN
- Inflammation

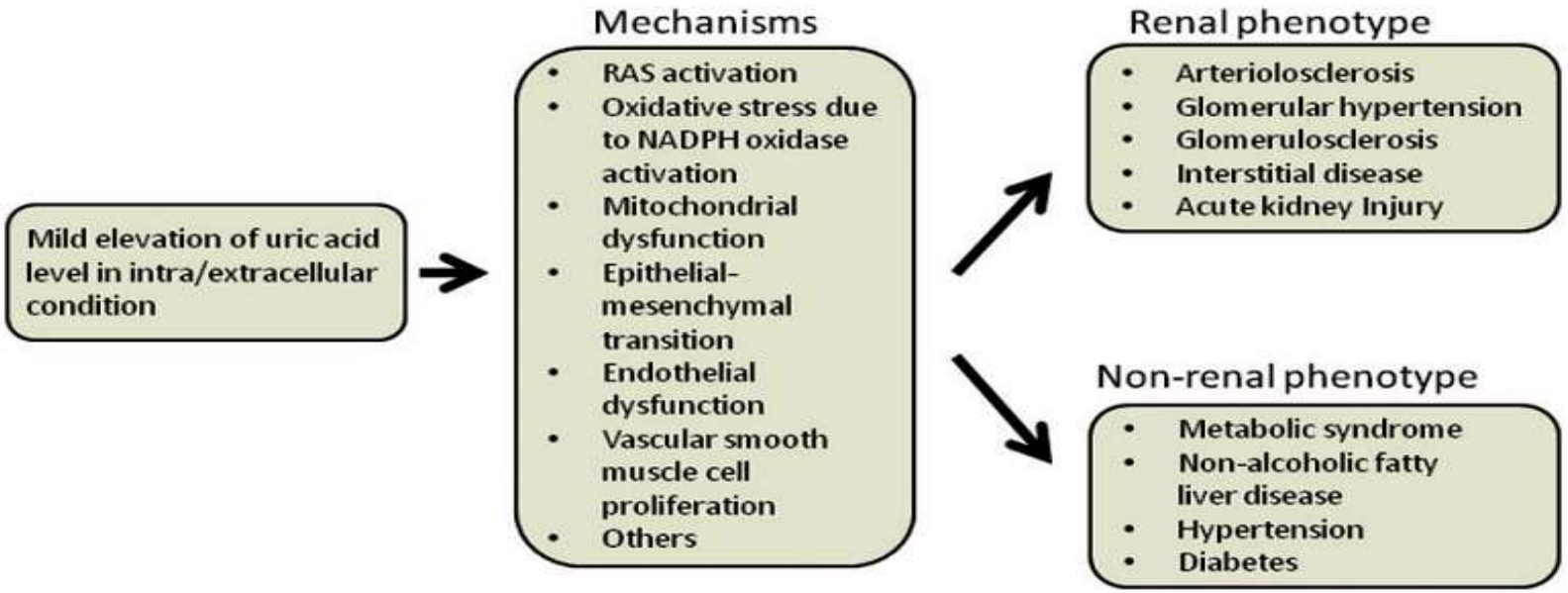
Pathophysiology

Nephrol Dial Transplant (2013) 28: 2221–2228
doi: 10.1093/ndt/gft029
Advance Access publication 29 March 2013

ndt
Nephrology Dialysis Transplantation

Full Reviews

Uric acid and chronic kidney disease: which is chasing which?



Circ J. 2015 Aug 21. [Epub ahead of print]

High Concentrations of Uric Acid Inhibit Angiogenesis via Regulation of the Krüppel-Like Factor 2-Vascular Endothelial Growth Factor-A Axis by miR-92a.

Yu S[1], Hong Q, Wang Y, Hou K, Wang L, Zhang Y, Fu B, Zhou Y, Zheng W, Chen X, Wu D.

Author information

Abstract

BACKGROUND: Angiogenesis is a critical component of many pathological conditions, and microRNAs (miRNAs) are indispensable in angiogenesis. It is unclear whether miRNAs regulate angiogenesis in the presence of high concentrations of uric acid (HUA), and the underlying mechanisms remain unknown.Methods and Results:It was found that HUA inhibited the angiogenic ability of endothelial cells. miRNA expression profiling was conducted using microarray assays in HUA-stimulated endothelial cells. Eighteen differentially expressed miRNAs were subjected to bioinformatic analyses. The results indicated that miR-92a was negatively regulated and was closely related to angiogenesis. Furthermore, the effects of miR-92a on HUA-stimulated endothelial cell angiogenesis and the underlying mechanisms were investigated in dual-luciferase reporter assays, electrophoretic mobility shift assays, immunoblot assays, and tube formation assays. It was determined that Krüppel-like factor 2 (KLF2) is a target gene of miR-92a, and KLF2 binds the vascular endothelial growth factor-A (VEGFA) promoter to inhibit its expression. miR-92a and VEGFA overexpression or KLF2 downregulation alleviates the HUA-mediated inhibition of angiogenesis in endothelial cells in vitro.

CONCLUSIONS: This study reported that there is a novel pathway regulating angiogenesis under HUA conditions. In the presence of HUA, miR-92a downregulation increased KLF2 expression, subsequently inhibiting VEGFA, which resulted in decreased angiogenesis. Thus, this study reports a possible mechanism for cardiovascular injury caused by hyperuricemia and suggests that the miR-92a-KLF2-VEGFA axis may be a target for hyperuricemia treatment.

Evidence

Eur J Intern Med. 2015 Aug 20. pii: S0953-6205(15)00223-X. doi: 10.1016/j.ejim.2015.06.016. [Epub ahead of print]

Clinical implications and outcome prediction in chronic hemodialysis patients with lower serum potassium×uric acid product.

Jiang MY[1], Hwang JC[2], Liu YH[1], Wang CL[1]

Author information

Abstract

BACKGROUND: The aims of this study were to evaluate correlations between serum potassium (S[K]) and uric acid (S[UA]) in hemodialysis patients and to determine whether lower levels of both S[K] and S[UA] were associated with poor long-term prognoses in these patients.

METHODS: A cohort of 424 maintenance hemodialysis patients (58±13years of age; 47% male; 39% with diabetes) from a single center were divided into tertiles based on the product of S[K]×S[UA] (K×UA). Group 1, low K×UA, n=141, Group 2, median K×UA, n=141, and Group 3, high K×UA; n=142. The longest observation period was 60months.

RESULTS: S[K] showed a positive linear correlation with S[UA] (r=0.33; p<0.001). In multivariate logistic regression analysis, Group 1 was characterized by hypoalbuminemia (odds ratio [OR]=0.20, 95% confidence interval (CI)=0.11-0.35) and lower levels of normalized protein catabolism [nPCR] (OR=0.10, 95%CI=0.05-0.22) and phosphate levels (OR=0.41, 95%CI=0.33-0.51). In contrast, Group 3 was associated with higher nPCR (OR=6.07, 95%CI=2.93-12.50) and albumin levels (OR=2.12, 95% CI=2.12-7.00). Compared to the reference (Group 1), the hazard ratio (HR) for long-term mortality was significantly lower in Groups 2 (HR=0.65, 95%CI=0.43-0.99) and 3 (HR=0.56, 95%CI=0.36-0.89). In multivariate Cox proportional analysis, the risk of mortality decreased by 2% (HR=0.98; 95%CI=0.96-0.99) per 1 unit increase in K×UA product.

CONCLUSION: Hemodialysis patients with lower S[K] and [UA] levels were characterized by hypoalbuminemia and lower nPCR, and they were associated with a long-term mortality risk.

J Cardiothorac Vasc Anesth. 2014 Dec;28(6):1440-7. doi: 10.1053/j.jvca.2014.04.020. Epub 2014 Sep 20.

Association of preoperative uric acid and acute kidney injury following cardiovascular surgery.

Joung KW[1], Jo JY[1], Kim WJ[1], Choi DK[1], Chin JH[1], Lee EH[2], Choi IC[1].

Author information

Abstract

OBJECTIVE: Recent studies suggested that elevated serum uric acid levels may be associated with the risk of acute kidney injury (AKI) in several settings. However, the effect of uric acid on the risk of AKI after cardiovascular surgery remains uncertain.

DESIGN: A retrospective analysis.

SETTING: A tertiary care university hospital.

PARTICIPANTS: All consecutive adult patients (n = 1,019) who underwent cardiovascular surgery between January 2011 and May 2012.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Preoperative and perioperative data were assessed in the study population. AKI was defined and staged as serum creatinine concentration-based Acute Kidney Injury Network criteria. Univariate and multivariate logistic regression analyses were conducted to evaluate the association between preoperative uric acid and postoperative AKI. Preoperative elevated uric acid (≥ 6.5 mg/dL) was associated independently with AKI after cardiovascular surgery (odds ratio 1.46; 95% confidence interval 1.04-2.06, p = 0.030). Results were the same in subgroup analyses. Preoperative elevated uric acid (≥ 6.5 mg/dL) also was associated with a higher incidence of prolonged ICU and hospital stay.

CONCLUSIONS: Preoperative elevated serum uric acid is an independent risk factor for AKI in patients undergoing cardiovascular surgery. This finding suggests that preoperative measurements of serum uric acid concentration may help stratify risks for AKI in these patients.

IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2015; 12(7): 599-604. doi: 10.7150/ijms.12106

Research Paper

Incidence and Risk Factors of Acute Kidney Injury after Radical Cystectomy: Importance of Preoperative Serum Uric Acid Level

Results: Of the 238 patients who met the eligibility criteria, 91 (38.2%) developed AKI. Univariate logistic regression analyses showed that male gender, high serum uric acid level, and long operation time associated with the development of AKI. On multivariate logistic regression analysis, preoperative serum uric acid concentration (odds ratio [OR] = 1.251; 95% confidence interval [CI] = 1.048–1.493; P = 0.013) and operation time (OR = 1.005; 95% CI = 1.002–1.008; P = 0.003) remained as independent predictors of AKI after radical cystectomy.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 732317, 10 pages
http://dx.doi.org/10.1155/2015/732317

Research Article

Use of Contrast-Enhanced Ultrasound to Study Relationship between Serum Uric Acid and Renal Microvascular Perfusion in Diabetic Kidney Disease

Purpose. To investigate the relationship between uric acid and renal microvascular perfusion in diabetic kidney disease (DKD) using contrast-enhanced ultrasound (CEUS) method. *Materials and Methods.* 79 DKD patients and 26 healthy volunteers were enrolled. Renal function and urine protein markers were tested. DKD patients were subdivided into two groups including a normal serum uric acid (SUA) group and a high SUA group. Contrast-enhanced ultrasound (CEUS) was performed, and low acoustic power contrast-specific imaging was used for quantitative analysis. *Results.* Normal controls (NCs) had the highest levels of AUC, AUC1, and AUC2. Compared to the normal SUA DKD group, high SUA DKD patients had significantly higher IMAX, AUC, and AUC1 ($P < 0.05$). DKD patients with low urinary uric acid (UUA) excretion had significantly higher AUC2 compared to DKD patients with normal UUA ($P < 0.05$). *Conclusion.* Hyperuricemia in DKD patients was associated with a renal ultrasound image suggestive of microvascular hyperperfusion. The CEUS parameter AUC1 holds promise as an indicator for renal microvascular hyperperfusion, while AUC2 might be a useful indicator of declining glomerular filtration rate in DKD patients with decreased excretion of uric acid.

Kidney & Blood Pressure Research

Kidney Blood Press Res 2013;37:181-189
DOI: 10.1159/000350143
Published online: Mai 21, 2013
Accepted: April 12, 2013

1423-0143/13/0373-0181$38.00/0

Original Paper

Uric Acid Levels and All-Cause Mortality in Peritoneal Dialysis Patients

Conclusion

Our results demonstrate that in PD patients, a higher serum UA level is related to increased mortality and is an independent risk factor for all-cause mortality. The presence of other comorbidities such as DM or malnutrition may elevate mortality in PD patients with lower serum UA. To confirm this relationship and to clarify the underlying mechanisms, additional studies in larger PD populations should be conducted.

Kidney & Blood Pressure Research

Kidney Blood Press Res 2015;40:315-322
DOI: 10.1159/000368507
Published online: June 08, 2015
Accepted: April 22, 2015
1423-0143/15/0403-0315$39.50/0

Original Paper

Relationship Between Serum Uric Acid Levels and Intrarenal Hemodynamic Parameters

inulin (C_{in}). ***Methods:*** Renal and glomerular hemodynamics were assessed by simultaneous measurement of C_{PAH} and C_{in} in 58 subjects. Of these, 19 subjects were planned to provide a kidney for transplantation; 26 had diabetes without proteinuria; and 13 had mild proteinuria. Renal and glomerular hemodynamics were calculated using Gomez`s formulae. ***Results:*** C_{in} was more than 60 ml/min/1.73m^2 in all subjects. Serum uric acid levels correlated significantly with vascular resistance at the afferent arteriole (R_a) ($r = 0.354$, $p = 0.006$), but not with that of the efferent arteriole (R_e). Serum uric acid levels ($\beta = 0.581$, $p = <0.001$) were significantly and independently associated with R_a after adjustment for several confounders ($R^2 = 0.518$, $p = <0.001$). ***Conclusions:*** These findings suggest, for the first time in humans, that higher serum uric acid levels are associated significantly with R_a in subjects with C_{in} > 60 ml/min/1.73m^2.

Hyperuricemia and the Progression of Chronic Kidney Disease: Is Uric Acid a Marker or an Independent Risk Factor?

Advances in Chronic Kidney Disease, Vol 19, No 6 (November), 2012: pp 386-391

Table 1. Summary of the Level of Evidence of the Association of Uric Acid With CKD

Type of Study	Evidence of Association
Animal models	Yes
Cross-sectional	Yes
Incident CKD	Mixed, but most studies show a positive association
Progression of established kidney disease	Most studies show a negative association
Transplantation graft loss/graft function	Most studies show a negative association (those that controlled for baseline kidney function)

- Marker in subtle renal injury
- Risk factor in early CKD(1,2) not late CKD(3-5)

Nephro Urol Mon. 2015 May; 7(3): e27233. DOI: 10.5812/numonthly.7(3)2015.27233

Published online 2015 May 23. **Review Article**

Associations Between Hyperuricemia and Chronic Kidney Disease: A Review

Nephrol Dial Transplant (2015) 0: 1–7
doi: 10.1093/ndt/gfv225

ndt
Nephrology Dialysis Transplantation

Original Article

Uric acid is not associated with decline in renal function or time to renal replacement therapy initiation in a referred cohort of patients with Stage III, IV and V chronic kidney disease

Methods. We analysed data in the Swedish Renal Registry–Chronic Kidney Disease (SRR-CKD), which is a nationwide registry of referred CKD patients. Patients with a visit between January 1st, 2005 and December 31st, 2011 were followed until

Results. There were 2466 patients

Conclusion. UA is not associated with the rate of decline in renal function or time to start of RRT in Stage III, IV and/or V CKD patients.

Renal Tx

World Journal of Nephrology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5527/wjn.v4.i3.324

World J Nephrol 2015 July 6; 4(3): 324-329
ISSN 2220-6124 (online)

EDITORIAL

Asymptomatic hyperuricemia following renal transplantation

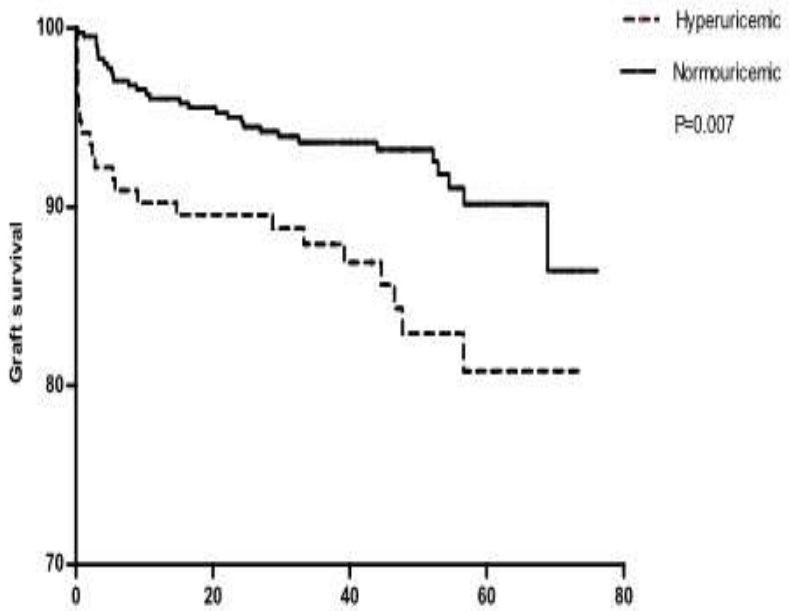
following renal transplantation. The prevalence of hyperuricemia in recipients of a renal allograft has been shown to range from 19% to 55% in patients whose immunosuppressive regimen did not include cyclosporin A (CsA) and from 30% to 84% in patients treated with CsA[7]. In the same series, incident gout was not observed in non-CsA treated patients, whereas it ranged from 2.0% to 28% following CsA therapy. More

- Evidence supports No ttt unless symptomatic or UA level ≥ 8

RESEARCH ARTICLE

Serum Uric Acid and Renal Transplantation Outcomes: At Least 3-Year Post-transplant Retrospective Multivariate Analysis

PLOS ONE | DOI:10.1371/journal.pone.0133834 July 24, 2015



Number at risk					
Normouricemic	418	400	393	388	0
Hyperuricemic	154	138	135	131	0

- Significant association between serum UA level and poor outcomes after adjustment for confounders including infection and rejection episode.
- Early stage post-transplant UA level can act as a predictor for renal function at multiple time points after transplant (up to 6m).

Curr Rheumatol Rep (2015) 17:13
DOI 10.1007/s11926-015-0495-2

CRYSTAL ARTHRITIS (MH PILLINGER AND S KRASNOKUTSKY, SECTION EDITORS)

Hyperuricemia, Gout, and Cardiovascular Disease: An Update

Aryeh M. Abeles

While hyperuricemia alone does not appear to confer an increased risk of stroke [21•], there appears to be an association between gout and cerebrovascular accidents. Recent stud-

There have been no placebo-controlled clinical trials studying the effects of urate-lowering therapy on CV outcomes in asymptomatic hyperuricemia. Given the absence of any data, and the potential risks of treatment, treating asymptomatic hyperuricemia for the purpose of improving CV outcomes is not recommended [28].

Richette, P. *et al. Nat. Rev. Rheumatol.* advance online publication 19 August 2014

Improving cardiovascular and renal outcomes in gout: what should we target?

Pascal Richette, Fernando Perez-Ruiz, Michael Doherty, Tim L. Jansen, George Nuki, Eliseo Pascual, Leonardo Punzi, Alexander K. So and Thomas Bardin

The risk of incident cardiovascular complications associated with hyperuricaemia in the absence of overt gout seems to be weaker. Observations from the Framingham Heart Study did not support a causal role for asymptomatic

Of note, a U-shaped association between SUA levels and both all-cause and cardiovascular mortality was reported in a cohort of 354,110 individuals without gout—and therefore not receiving any treatment for this disease—indicating that not only high but very low SUA levels might increase mortality risk.[4]

AJKD
Am J Kidney Dis. 2015;66(6):933-935
Editorial

Is It Time to Start Treating Asymptomatic Hyperuricemia?

studies that suggest that hyperuricemia is not a benign condition and that urate-lowering therapy can mitigate kidney function decline. Given the favorable side-effect profile of urate-lowering therapy and the renal, cardiovascular, and cerebrovascular benefits from normalizing serum uric acid levels, the question should not be if, but rather when, patients with hyperuricemia should be treated. Obermayer et al[6] may provide some guidance for when to initiate urate-lowering therapy in patients with asymptomatic hyperuricemic, noting that a serum uric acid level > 9 mg/dL carries a 3-fold risk for kidney disease. Further

International Journal of Rheumatic Diseases 2015; 18: 341–351

ORIGINAL ARTICLE

Australian and New Zealand recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion in the 3e Initiative

Recommendation 9

At present, there is insufficient evidence to recommend treatment of asymptomatic hyperuricemia to prevent gouty arthritis, renal disease or cardiovascular events.

Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative

2	In patients with gout and/or hyperuricaemia, renal function should be measured and assessment of cardiovascular risk factors is recommended	
10	Pharmacological treatment of asymptomatic hyperuricaemia is not recommended to prevent gouty arthritis, renal disease or CV events	2b

Although there was an absence of evidence supporting the use of ULT for asymptomatic hyperuricaemia, experts agreed that lifestyle advice on diet, weight loss or exercise would apply to patients with asymptomatic hyperuricaemia, especially after

Sivera F, *et al*. *Ann Rheum Dis* 2014;**73**:328–335

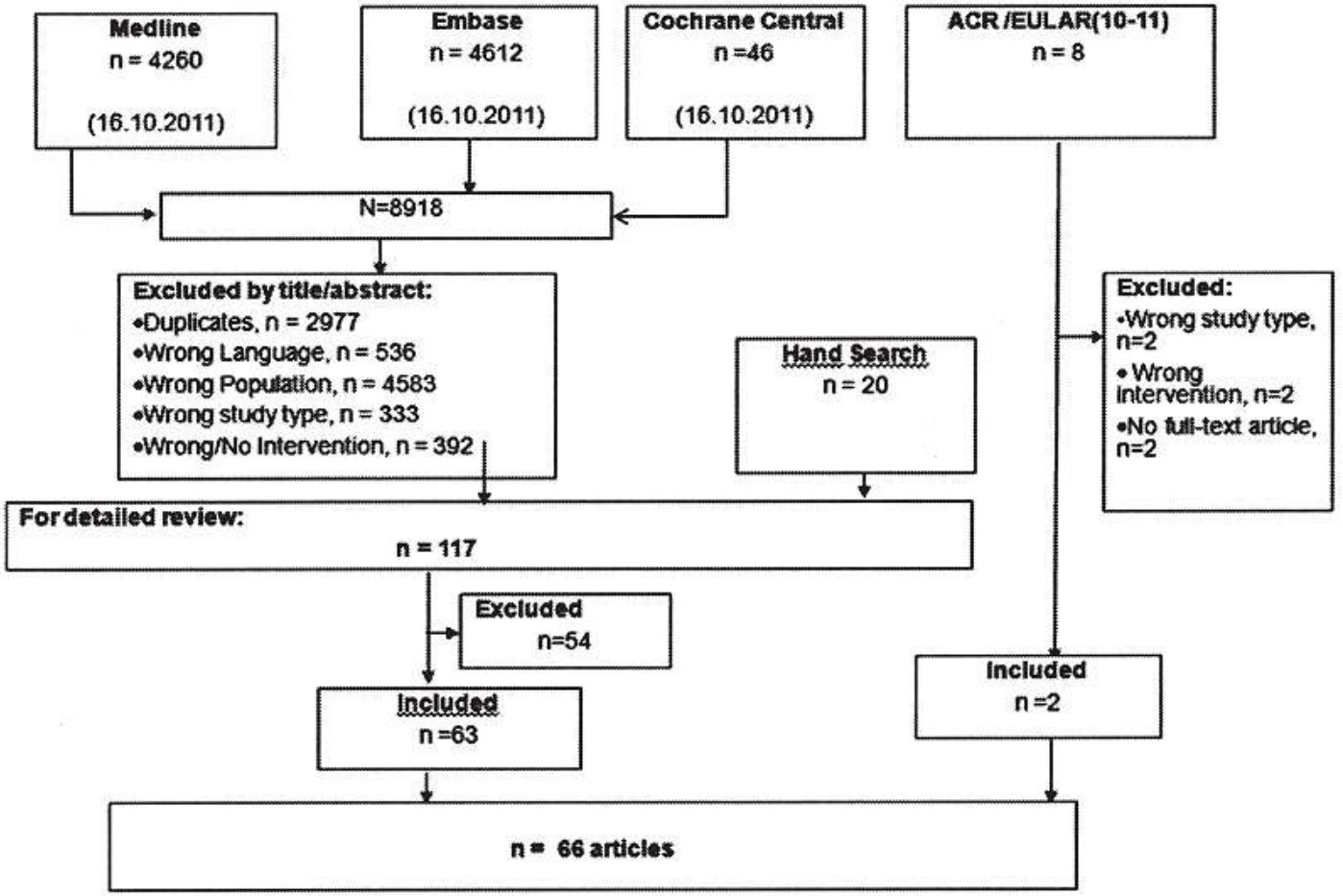
Allopurinol treatment improves renal function in patients with type 2 diabetes and asymptomatic hyperuricemia: a three years of randomized parallel-controlled study

Methods: Application of randomized open parallel-controlled methods, a total of 176 patients with type 2 diabetes and asymptomatic hyperuricemia were selected

Results: There were no statistically significant difference in the baseline clinical characteristics of study participants between two treatment groups ($p>0.05$ for all).

Conclusion: Long-term effective control of serum uric acid can decrease UAER and serum creatinine, increase GFR, and may exert kidney protection effects in patients with type 2 diabetes and asymptomatic hyperuricemia.

Cardiovascular Risk Factors and Comorbidities in Patients with Hyperuricemia and/or Gout: A Systematic Review of the Literature



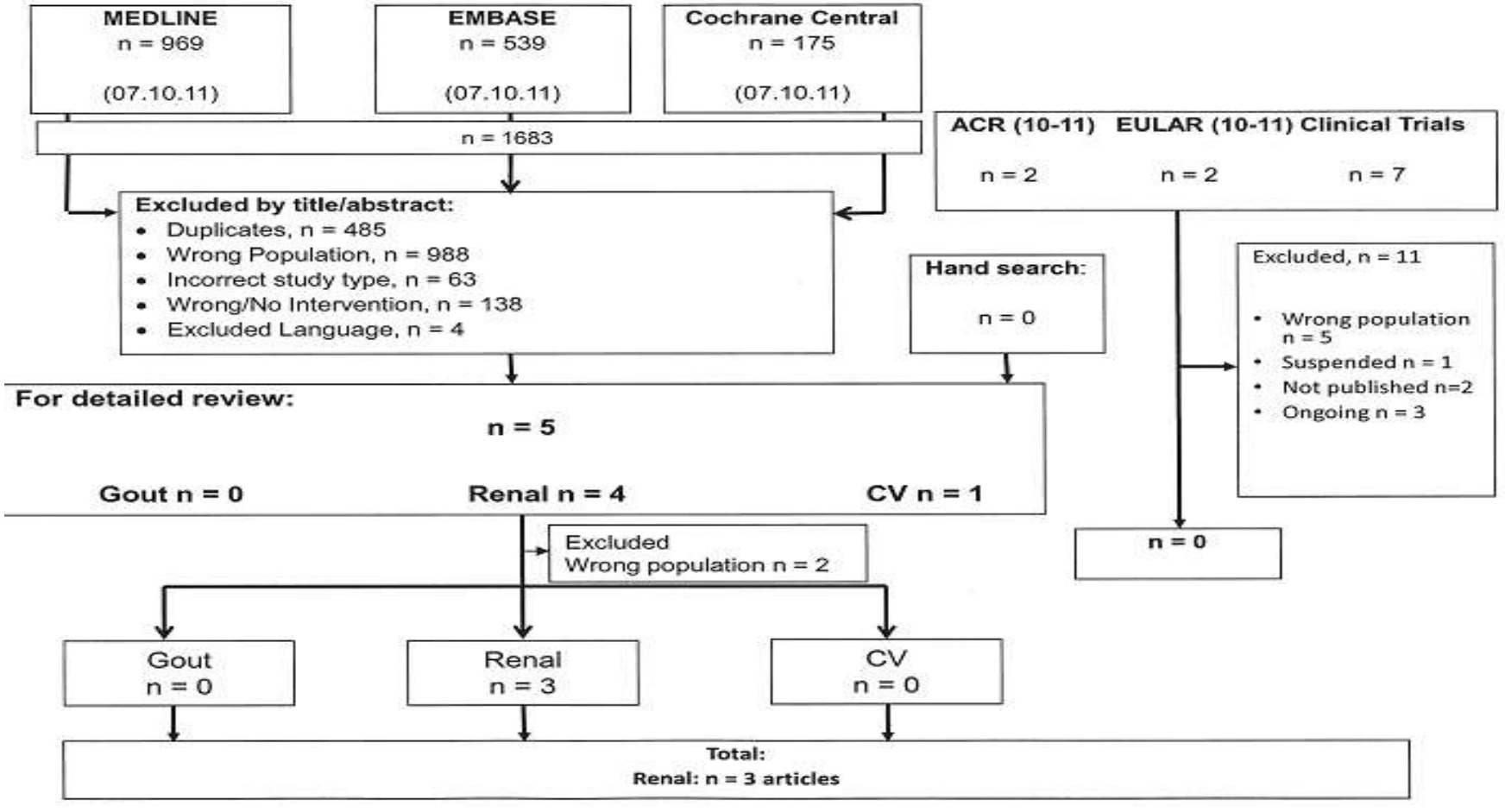
The Journal of Rheumatology Supplement 2014; 41 Suppl 92;

Cardiovascular Risk Factors and Comorbidities in Patients with Hyperuricemia and/or Gout: A Systematic Review of the Literature

In summary, the well-grounded assumption that gout and hyperuricemia are risk factors for clinically manifest CV disease is based mainly on cross-sectional association studies. In the prospective cohort studies we analyzed in this review, the risk did not seem to be increased at all or was shown to be only slightly increased. Another important finding of our review is that, if an increased risk of CV disease was found in univariate analysis, this increased risk disappeared or at least was drastically lowered after adjustment for confounders. This may suggest that hyperuricemia should be seen as a risk indicator (and part of the metabolic syndrome) rather than as an individual and independent risk factor.

The Journal of Rheumatology Supplement 2014; 41 Suppl 92;

Treatment of Asymptomatic Hyperuricemia for the Prevention of Gouty Arthritis, Renal Disease, and Cardiovascular Events: A Systematic Literature Review



The Journal of Rheumatology Supplement 2014; 41 Suppl 92;

Treatment of Asymptomatic Hyperuricemia for the Prevention of Gouty Arthritis, Renal Disease, and Cardiovascular Events: A Systematic Literature Review

empiric data, the 2012 ACR guidelines for management of gout did not address the pharmacological management of asymptomatic HU[21].

CV events has also been described. However, the available interventional data on treating HU in asymptomatic patients is extremely sparse and fraught with limitations. Therefore, pharmacological treatment of asymptomatic hyperuricemia cannot be recommended at present for the prevention of gouty arthritis, renal disease, or CV events. Further inter-

The Journal of Rheumatology Supplement 2014; 41 Suppl 92;

The Effects of Allopurinol on the Carotid Intima-media Thickness in Patients with Type 2 Diabetes and Asymptomatic Hyperuricemia: A Three-year Randomized Parallel-controlled Study

Intern Med 54: 2129-2137, 2015

Methods This was a randomized open parallel-controlled study. In this study, 176 patients with T2DM and asymptomatic HUA were randomly allocated to the conventional or allopurinol treatment groups on the basis

Results There were no statistically significant differences in the baseline characteristics of the study participants between the two treatment groups ($p>0.05$ for all). Nevertheless, the serum uric acid, triglyceride, and

Conclusion

This study demonstrated that positive and effective control of the serum uric acid level may improve insulin resistance, decrease the serum levels of TG, hs-CRP, control blood pressure, and reduce the carotid IMT, thereby delaying the development of atherosclerosis in patients with T2DH and asymptomatic HUA.

To Treat or Not to Treat Asymptomatic Hyperuricemia

Hamid Mustafa

Department of Medicine, Umm Al-Qura University, Makkah, Kingdom of Saudi Arabia

Materials and Methods: This survey was carried out using a structured questionnaire that was answered through face-to-face interviews with 104 physicians who diagnose and treat hyperuricemia. The data was collected on the second half of 2012. The specialties included in the study were general practitioners, family physicians, orthopedicians and rheumatologists.

Conclusions: The results showed that the doctors in Makkah Region depend on the serum uric acid levels to decide when to start the treatment, not abiding by the international guidelines. They still chose the life-style and dietary modification, as well as starting treatment with allopurinol with a starting dose of 100 mg/dL daily.

REVIEW

H. ERHAN DINCER, MD
Department of Medicine, Michael Reese Hospital and Medical Center, Chicago

AYSE P. DINCER, MD
Department of Medicine, Mercy Hospital and Medical Center, Chicago

DENNIS J. LEVINSON, MD
Department of Medicine, Michael Reese Hospital and Medical Center, Chicago

Asymptomatic hyperuricemia: To treat or not to treat

WHEN TO CONSIDER TREATMENT

Patients about to receive chemotherapy

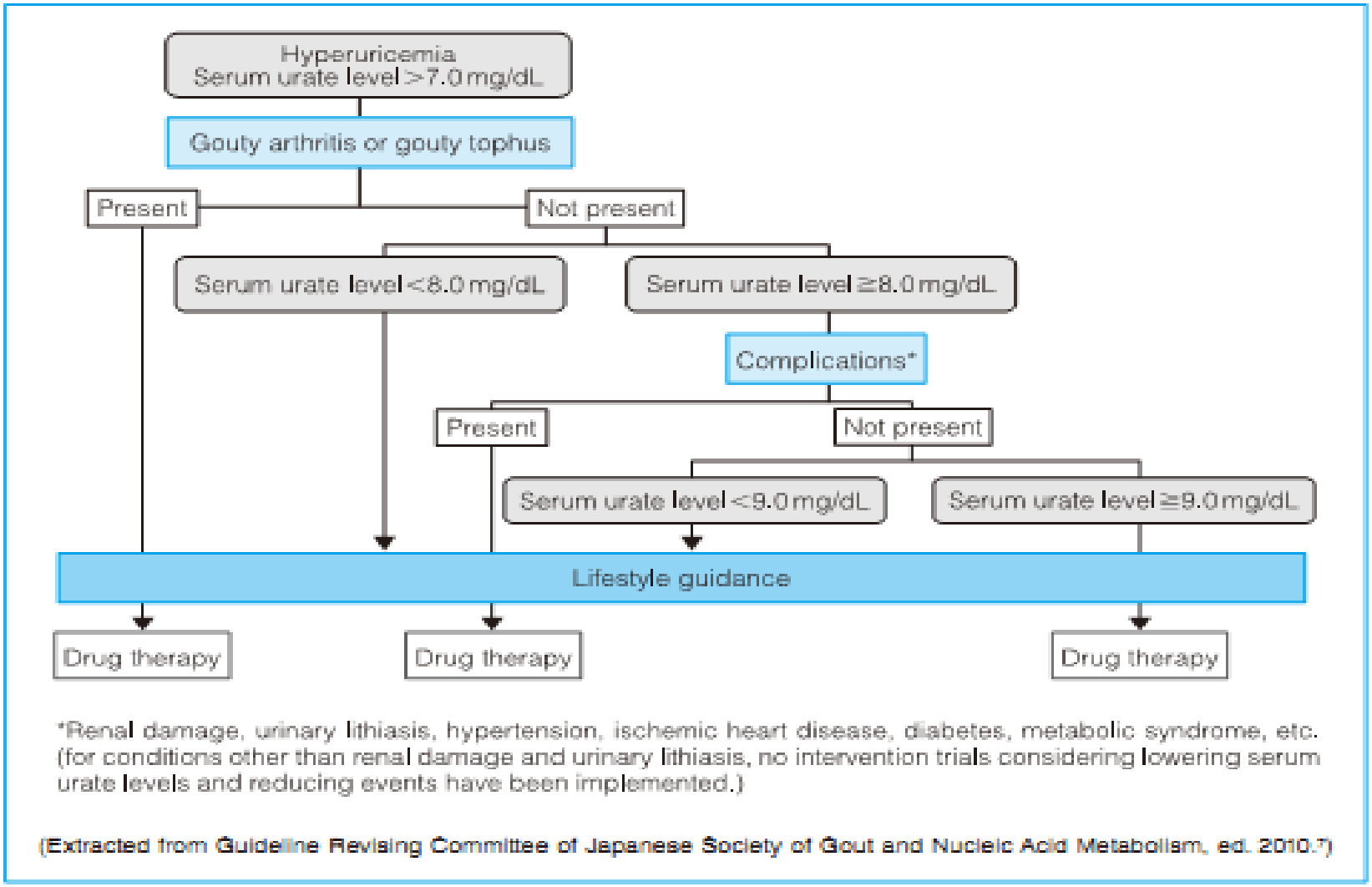
Patients with a history of kidney stones

Patients with a history of gouty attacks, tophi, and moderate renal functional impairment

Patients with very high levels of uric acid

Essence of the Revised Guideline for the Management of Hyperuricemia and Gout

JMAJ 55(4): 324–329, 2012



*Renal damage, urinary lithiasis, hypertension, ischemic heart disease, diabetes, metabolic syndrome, etc. (for conditions other than renal damage and urinary lithiasis, no intervention trials considering lowering serum urate levels and reducing events have been implemented.)

(Extracted from Guideline Revising Committee of Japanese Society of Gout and Nucleic Acid Metabolism, ed. 2010.[7])

Essence of the Revised Guideline for the Management of Hyperuricemia and Gout

JMAJ 55(4): 324–329, 2012

Treatment of hyperuricemia (Fig. 2)

(1) What is most important in the treatment of hyperuricemia is the improvement of lifestyle habits that are related to the development of hyperuricemia and which also easily lead to the development of prognosis-related complications such as obesity, hypertension, and lipid metabolism abnormalities. **Recommendation level A**

(2) Drug therapy is indicated in cases where gouty arthritis occurs repeatedly or gouty tophus is diagnosed, and maintenance of serum urate levels of 6.0 mg/dL or lower is desirable.

Recommendation level A

(3) Drug therapy for asymptomatic hyperuricemia is implemented when serum urate levels are 8.0 mg/dL or higher as a general indicator, but should be undertaken with caution. **Recommendation level C**

TTT

Table 4 Urate lowering drugs

Pharmacologic options for the treatment of hyperuricemia

Xanthine-oxidase inhibitors: Allopurinol, febuxostat

Uricosuric agents: Probenecid, sulfinpyrazone, benzbromarone

Uricase: Rasburicase, pegloticase

Drugs and contrast media with hypouricemic properties, not primarily intended for the treatment of hyperuricemia

Acetohexamide, azauridine, chlorprothixene, dicumarol, estrogens, fenofibrate, glyceryl guaiacolate, iopanoic acid, losartan, meglumine iodipamide, phenylbutazone, salicylates and other NSAIDs, sodium diatrizoate, trimetoprim-sulfamethoxazole

Am J Kidney Dis. 2006 Jan;47(1):51-9.

Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level.

Siu YP[1], Leung KT, Tong MK, Kwan TH.

⊕ Author information

Abstract

BACKGROUND: Hyperuricemia is associated strongly with the development of hypertension, renal disease, and progression. Allopurinol decreases serum uric acid levels by inhibiting the enzyme xanthine oxidase. We hypothesized that administrating allopurinol to decrease serum uric acid levels to the normal range in hyperuricemic patients with chronic kidney disease may be of benefit in decreasing blood pressure and slowing the rate of renal disease progression in these patients.

METHODS: We conducted a prospective, randomized, controlled trial of 54 hyperuricemic patients with chronic kidney disease. Patients were randomly assigned to treatment with allopurinol, 100 to 300 mg/d, or to continue the usual therapy for 12 months. Clinical, hematologic, and biochemical parameters were measured at baseline and 3, 6, and 12 months of treatment. We define our study end points as: (1) stable kidney function with less than 40% increase in serum creatinine level, (2) impaired renal function with creatinine level increase greater than 40% of baseline value, (3) initiation of dialysis therapy, and (4) death.

RESULTS: One patient in the treatment group dropped out because of skin allergy to allopurinol. Serum uric acid levels were significantly decreased in subjects treated with allopurinol, from 9.75 +/- 1.18 mg/dL (0.58 +/- 0.07 mmol/L) to 5.88 +/- 1.01 mg/dL (0.35 +/- 0.06 mmol/L; $P < 0.001$). There were no significant differences in systolic or diastolic blood pressure at the end of the study comparing the 2 groups. There was a trend toward a lower serum creatinine level in the treatment group compared with controls after 12 months of therapy, although it did not reach statistical significance ($P = 0.08$). Overall, 4 of 25 patients (16%) in the allopurinol group reached the combined end points of significant deterioration in renal function and dialysis dependence compared with 12 of 26 patients (46.1%) in the control group ($P = 0.015$).

CONCLUSION: Allopurinol therapy significantly decreases serum uric acid levels in hyperuricemic patients with mild to moderate chronic kidney disease. Its use is safe and helps preserve kidney function during 12 months of therapy compared with controls. Results of this study need to be confirmed with an additional prospective trial involving a larger cohort of patients to determine the long-term efficacy of allopurinol therapy and in specific chronic kidney disease subpopulations.

Am J Kidney Dis. 2015 Jul 30. pii: S0272-6386(15)00846-X. doi: 10.1053/j.ajkd.2015.05.017. [Epub ahead of print]

Efficacy of Febuxostat for Slowing the GFR Decline in Patients With CKD and Asymptomatic Hyperuricemia: A 6-Month, Double-Blind, Randomized, Placebo-Controlled Trial.

Sircar D[1], Chatterjee S[2], Waikhom R[3], Golay V[4], Raychaudhury A[4], Chatterjee S[2], Pandey R[4].

Author information

Abstract

BACKGROUND: Hyperuricemia is a putative risk factor for the progression of chronic kidney disease (CKD). We hypothesized that control of asymptomatic hyperuricemia may slow disease progression in CKD.

STUDY DESIGN: This was a single-center, double-blind, randomized, parallel-group, placebo-controlled study.

SETTING & PARTICIPANTS: Eligible participants were adults from Eastern India aged 18 to 65 years with CKD stages 3 and 4, with asymptomatic hyperuricemia.

INTERVENTION: The intervention group received febuxostat, 40mg, once daily for 6 months, while the placebo group received placebo; both groups were followed up for 6 months.

OUTCOMES: The primary outcome was the proportion of patients showing a >10% decline in estimated glomerular filtration rate (eGFR) from baseline in the febuxostat and placebo groups. Secondary outcomes included changes in eGFRs in the 2 groups from baseline and at the end of the study period.

RESULTS: 45 patients in the febuxostat group and 48 in the placebo group were analyzed. Mean eGFR in the febuxostat group showed a nonsignificant increase from 31.5±13.6 (SD) to 33.7±16.6mL/min/1.73m^2 at 6 months. With placebo, mean eGFR decreased from a baseline of 32.6±11.6 to 28.2±11.5mL/min/1.73m^2 (P=0.003). The difference between groups was 6.5 (95% CI, 0.08-12.81) mL/min/1.73m^2 at 6 months (P=0.05). 17 of 45 (38%) participants in the febuxostat group had a >10% decline in eGFR over baseline compared with 26 of 48 (54%) from the placebo group (P<0.004).

Ann Oncol. 2015 Jul 27. pii: mdv317. [Epub ahead of print]

FLORENCE: a randomized, double-blind, phase III pivotal study of febuxostat versus allopurinol for the prevention of tumor lysis syndrome (TLS) in patients with hematologic malignancies at intermediate to high TLS risk.

Spina M[1], Nagy Z[2], Ribera JM[3], Federico M[4], Aurer I[5], Jordan K[6], Borsaru G[7], Pristupa AS[8], Bosi A[9], Grosicki S[10], Glushko NL[11], Ristic D[12], Jakucs J[13], Montesinos P[14], Mayer J[15], Rego EM[16], Baldini S[17], Scartoni S[17], Capriati A[17], Maggi CA[17], Simonelli C; FLORENCE Study Group.

⊕ Author information

Abstract

BACKGROUND: Serum uric acid (sUA) control is of key relevance in tumor lysis syndrome (TLS) prevention as it correlates with both TLS and renal event risk. We sought to determine whether febuxostat fixed dose achieves a better sUA control than allopurinol while preserving renal function in TLS prevention.

PATIENTS AND METHODS: Patients with hematologic malignancies at intermediate to high TLS risk grade were randomized to receive febuxostat or allopurinol, starting 2 days before induction chemotherapy, for 7-9 days. Study treatment was blinded, whereas daily dose (low/standard/high containing allopurinol 200/300/600 mg, respectively, or fixed febuxostat 120 mg) depended on the investigator's choice. The co-primary end points, sUA area under curve (AUC sUA_{1-8}) and serum creatinine change, were assessed from baseline to day 8 and analyzed through analysis of covariance with two-sided overall significance level of 5%. Secondary end points included treatment responder rate, laboratory and clinical TLS incidence and safety.

RESULTS: A total of 346 patients (82.1% intermediate TLS risk; 82.7% assigned to standard dose) were randomized. Mean AUC sUA_{1-8} was 514.0 ± 225.71 versus 708.0 ± 234.42 mgxh/dl ($P < 0.0001$) in favor of febuxostat. Mean serum creatinine change was -0.83 ± 26.98% and -4.92 ± 16.70% for febuxostat and allopurinol, respectively ($P = 0.0903$). No differences among secondary efficacy end points were detected. Drug-related adverse events occurred in 6.4% of patients in both arms.

CONCLUSION: In the largest adult trial carried out in TLS prevention, febuxostat achieved a significant superior sUA control with one fixed dose in comparison to allopurinol with comparable renal function preservation and safety profile.

Transplant Proc. 2014;46(2):511-3. doi: 10.1016/j.transproceed.2013.09.045.

Efficacy and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase for the treatment of hyperuricemia in kidney transplant recipients.

Tojimbara T[1], Nakajima I[2], Yashima J[3], Fuchinoue S[2], Teraoka S[3].

Author information

Abstract

BACKGROUND: Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase, is a potential alternative to allopurinol for patients with hyperuricemia. In this study, we evaluated the efficacy and safety of febuxostat for the management of hyperuricemia in renal transplant recipients.

PATIENTS AND METHODS: Between June 2012 and January 2013, a total of 22 renal transplant recipients (56 ± 10 years old) with hyperuricemia were enrolled in this study. All patients underwent de novo kidney transplantation, except for 1 patient, who received a second kidney transplant. Ten patients receiving allopurinol and 3 patients receiving benzbromarone were converted to febuxostat at doses of 10-20 mg/d. In the remaining 9 patients, who did not have a history of other urate-lowering medications, febuxostat was initiated at a dose of 10 mg/d.

RESULTS: Uric acid levels after initiation of febuxostat were significantly lower than before treatment (5.7 ± 0.7 mg/mL vs 8.0 ± 0.8 mg/mL; $P < .001$). At last follow-up visit, 16 of the 22 patients (73%) achieved uric acid levels of ≤ 6.0 mg/dL, despite the low dosage of febuxostat. All patients were maintained on febuxostat without serious adverse events, except for 1 patient, who discontinued febuxostat because of numbness in the arms.

CONCLUSIONS: Low-dose febuxostat is a promising alternative to allopurinol or benzbromarone for the treatment of hyperuricemia in kidney transplant recipients. The long-term urate-lowering efficacy and safety of febuxostat with regard to renal function in kidney transplant recipients with hyperuricemia requires further investigation.

Eur Rev Med Pharmacol Sci. 2007 May-Jun;11(3):179-84.

Is rasburicase an effective alternative to allopurinol for management of hyperuricemia in renal failure patients? A double blind-randomized study.

De Angelis S[1], Noce A, Di Renzo L, Cianci R, Naticchia A, Giarrizzo GF, Giordano F, Tozzo C, Splendiani G, De Lorenzo A.

Author information

Abstract

Recent epidemiological studies provide a clear evidence that hyperuricemia is associated with hypertension, coronary heart disease, left ventricular hypertrophy and progression of renal disease. Aim of our study was to assess the effect of low dosage of recombinant urate oxidase on hyperuricemia in renal failure patients that already receiving allopurinol. Our study group consisted of 43 renal failure patients, 23 women and 20 men. The mean age was 74 years (range 36-90 years). The following variables were studied on admission: serum creatinine, blood urea nitrogen and serum uric acid. Intravenous rasburicase was administered at a dose of 0.02 mg/kg/day on 3 consecutive days in patients with serum uric acid between 8-10 mg/dl, on 5 consecutive days in patients with serum uric acid between 10-15 mg/dl and on 7 consecutive days in patients with serum uric acid > 15 mg/dl. Uric acid levels were assayed after 48 hours and 7 days after rasburicase treatment. Mean values of uric acid levels after 48 hours were 2.47 mg/dl (+/- 1.58) in men and 2.77 mg/dl (+/- 2.24) in woman, where'as mean values of uric acid levels after 7 days were 4.45 mg/dl (+/- 2.0) in men and 5.75 mg/dl (+/- 1.9) in woman. No significant relationship were found between uric acid and creatinine as before as well after therapy. There were no side effects in all patients included in the study. After 7 days, the rasburicase therapy showed more antihyperuricemic effect in men (59%) than in women (46%).

EXPERT OPINION

Investigational drugs for hyperuricemia

Expert Opin. Investig. Drugs (2015) 24(8)

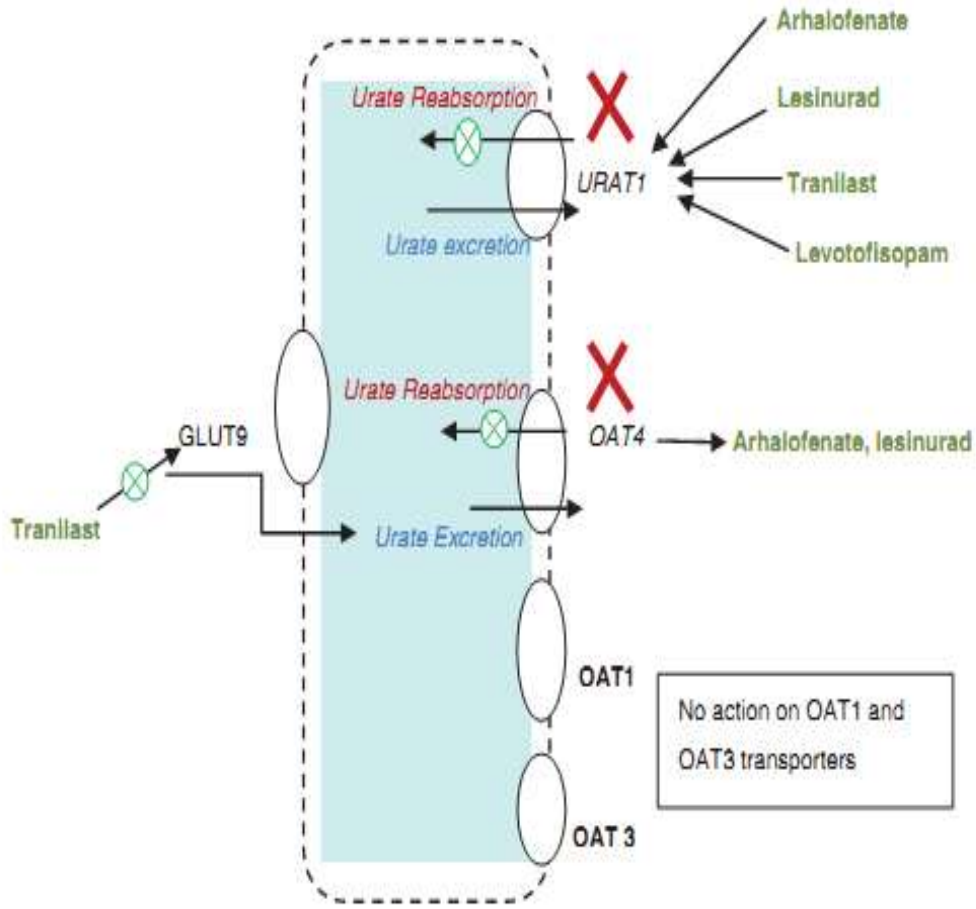
a) Inhibitors of reabsorption

b) Urate synthesis inhibitors:

- Ulodesine

c) Others:

- Marine active
- (IL-1) inhibitors: Anakinra-Canakinumab, rilonaept
- KX-1151(XO, URAT1 inhibitor)



Yao Xue Xue Bao. 2010 Oct;45(10):1239-46.

[Mangiferin promotes uric acid excretion and kidney function improvement and modulates related renal transporters in hyperuricemic mice].

[Article in Chinese]

Hu QH[1], Zhang X, Wang Y, Kong LD.

Author information

Abstract

The effects of mangiferin on uric acid excretion, kidney function and related renal transporters were investigated in hyperuricemic mice induced by potassium oxonate. Mice were divided into normal control group, and 5 hyperuricemic groups with model control, 50, 100, and 200 mg x kg(-1) mangiferin, and 5 mg x kg(-1) allopurinol. Mice were administered by gavage once daily with 250 mg x kg(-1) potassium oxonate for seven consecutive days to create the model. And 3 doses of mangiferin were orally initiated on the day 1 h after potassium oxonate was given, separately. Serum uric acid, creatinine and urea nitrogon levels, as well as urinary uric acid creatinine levels were measured. Mouse uromodulin (mUMOD) levels in serum, urine and kidney were determined by ELISA method. The mRNA and protein levels of related renal transporters were assayed by RT-PCR and Western blotting methods, respectively. Compared to model group, mangiferin significantly reduced serum uric acid, creatinine and urea nitrogon levels, increased 24 h uric acid and creatinine excretion, and fractional excretion of uric acid in hyperuricemic mice, exhibiting uric acid excretion enhancement and kidney function improvement. Mangiferin was found to down-regulate mRNA and protein levels of urate transporter 1 (mURAT1) and glucose transporter 9 (mGLUT9), as well as up-regulate organic anion transporter 1 (mOAT1) in the kidney of hyperuricemic mice. These findings suggested that mangiferin might enhance uric acid excretion and in turn reduce serum uric acid level through the decrease of uric acid reabsorption and the increase of uric acid secretion in hyperuricemic mice. Moreover, mangiferin remarkably up-regulated expression levels of renal organic cation and carnitine transporters (mOCT1, mOCT2, mOCTN1 and mOCTN2), increased urine mUMOD levels, as well as decreased serum and kidney mUMOD levels in hyperuricemic mice, which might be involved in mangiferin-mediated renal protective action.

Planta Med. 2011 May;77(8):786-94. doi: 10.1055/s-0030-1250599. Epub 2010 Dec 10.

Mulberroside a possesses potent uricosuric and nephroprotective effects in hyperuricemic mice.

Wang CP[1], Wang Y, Wang X, Zhang X, Ye JF, Hu LS, Kong LD.

Author information

Abstract

Mulberroside A is a major stilbene glycoside of MORUS ALBA L. (Moraceae), which is effectively used for the treatment of hyperuricemia and gout in traditional Chinese medicine. We examined whether mulberroside A had effects on renal urate underexcretion and dysfunction in oxonate-induced hyperuricemic mice and investigated the potential uricosuric and nephroprotective mechanisms involved. Mulberroside A at 10, 20, and 40 mg/kg decreased serum uric acid levels and increased urinary urate excretion and fractional excretion of uric acid in hyperuricemic mice. Simultaneously, it reduced serum levels of creatinine and urea nitrogen (10-40 mg/kg), urinary N-acetyl- β-D-glucosaminidase activity (10-40 mg/kg), β_2-microglobulin (10-40 mg/kg) and albumin (20-40 mg/kg), and increased creatinine clearance (10-40 mg/kg) in hyperuricemic mice. Furthermore, mulberroside A downregulated mRNA and protein levels of renal glucose transporter 9 (mGLUT9) and urate transporter 1 (mURAT1), and upregulated mRNA and protein levels of renal organic anion transporter 1 (mOAT1) and organic cation and carnitine transporters (mOCT1, mOCT2, mOCTN1, and mOCTN2) in hyperuricemic mice. This is the first study demonstrating that mulberroside A exhibits uricosuric and nephroprotective effects mediated in part by cooperative attenuation of the expression alterations of renal organic ion transporters in hyperuricemic mice. These data suggest that mulberroside A may be a new drug candidate for the treatment of hyperuricemia with renal dysfunction.

Chin J Nat Med. 2013 May;11(3):214-21. doi: 10.1016/S1875-5364(13)60019-9.

Wuling san ameliorates urate under-excretion and renal dysfunction in hyperuricemic mice.

Ding XQ[1], Pan Y, Wang X, Ma YX, Kong LD.

Author information

Abstract

AIM: The present study was undertaken to characterize the effects of Wuling San on urate excretion and renal function, and explore its possible mechanisms of action in hyperuricemic mice.

METHODS: Mice were administered with 250 mg·kg(-1) potassium oxonate by gavage once daily (10 animals/group) for seven consecutive days to develop a hyperuricemia model. Different doses of Wuling powder were orally initiated on the day 1 h after oxonate was given, separately. Allopurinol was used as a positive control. Serum and urine levels of uric acid and creatinine, and fractional excretion of uric acid (FEUA) were measured in hyperuricemic mice treated with Wuling San and allopurinol. Simultaneously, renal mRNA and protein levels of urate transporter 1 (mURAT1), glucose transporter 9 (mGLUT9), organic anion transporter 1 (mOAT1), as well as organic cation/carnitine transporters mOCT1, mOCT2 and mOCTN2, were assayed by semi-quantitative RT-PCR and Western blot methods, respectively.

RESULTS AND CONCLUSION: Compared to the hyperuricemia control group, Wuling San significantly reduced serum uric acid and creatinine levels, increased 24 h urate and creatinine excretion, and FEUA in hyperuricemic mice, exhibiting its ability to enhance urate excretion and improve kidney function. Wuling San was found to down-regulate mRNA and protein levels of mURAT1 and mGLUT9, as well as up-regulate mOAT1 in the kidney of hyperuricemic mice. Moreover, Wuling San up-regulated renal mRNA and protein levels of mOCT1, mOCT2 and mOCTN2, leading to kidney protection in this model.

Eur J Nutr. 2012 Aug;51(5):593-606. doi: 10.1007/s00394-011-0243-y. Epub 2011 Sep 10.

Quercetin regulates organic ion transporter and uromodulin expression and improves renal function in hyperuricemic mice.

Hu QH[1], Zhang X, Wang X, Jiao RQ, Kong LD.

Author information

Abstract

BACKGROUND: Renal organic ion transporters and uromodulin (UMOD) play the important roles in renal urate excretion and function. Hyperuricemia is considered as a risk factor for the development of renal dysfunction. The flavonoid quercetin in diets exerts the hypouricemic and nephroprotective effects.

PURPOSES: To evaluate the effects of quercetin on renal organic ion transporters and UMOD in hyperuricemic mice.

METHODS: Kun-Ming mice were divided into normal and hyperuricemic groups receiving water, 25, 50 and 100 mg/kg quercetin, 5 mg/kg allopurinol, respectively. Hyperuricemic mice were orally gavaged with 250 mg/kg oxonate daily for 1 week. Quercetin and allopurinol were orally gavaged on the day when oxonate or water was given 1 h later. After 1 week, serum uric acid, creatinine and blood urea nitrogen concentrations, excretion of urate and creatinine, and fractional excretion of uric acid were measured. The mRNA and protein levels of renal urate transporter 1 (mURAT1), glucose transporter 9 (mGLUT9), organic anion transporter 1 (mOAT1) and organic cation/carnitine transporters (mOCT1, mOCT2, mOCTN1 and mOCTN2) in mice were analyzed. Simultaneously, UMOD levels in serum, urine and kidney, as well as renal UMOD mRNA expression were detected.

RESULTS: Quercetin significantly restored oxonate-induced abnormalities of these biochemical indexes compared with normal vehicle group. Furthermore, it remarkably prevented expression changes of renal organic ion transporters and UMOD, and UMOD level alteration in hyperuricemic mice.

CONCLUSIONS: These results suggest that quercetin has the uricosuric and nephroprotective actions mediated by regulating the expression levels of renal organic ion transporters and UMOD.

J Hypertens. 2008 Dec;26(12):2326-38. doi: 10.1097/HJH.0b013e328312c8c1.

Activation of ATP-sensitive potassium channels protects vascular endothelial cells from hypertension and renal injury induced by hyperuricemia.

Long CL[1], Qin XC, Pan ZY, Chen K, Zhang YF, Cui WY, Liu GS, Wang H.

⊕ Author information

Abstract

BACKGROUND AND OBJECTIVES: It has been demonstrated that hyperuricemia induces reno-cardiovascular damage resulting in hypertension and renal injury because of vascular endothelial dysfunction. The pathogenesis of hyperuricemia, endothelial dysfunction, hypertension, and renal injury is progressive, and develops into a vicious cycle. It is reasonable to suggest that an antihypertensive drug with endothelial protection may block this vicious cycle. Iptakalim, a novel antihypertensive drug undergoing phase-three clinical trials, is a new ATP-sensitive potassium channel opener and can ameliorate endothelial dysfunction. We hypothesized that iptakalim could prevent hypertension and retard the pathogenesis of endothelial dysfunction and renal injury in hyperuricemic rats.

METHODS AND RESULTS: In rats with hyperuricemia induced by 2% oxonic acid and 0.1 mmol/l uric acid, iptakalim prevented increases in systolic blood pressure, reduced the impairment of endothelial vasodilator function, and attenuated renal dysfunction and pathological changes in glomerular and renal interstitial tissue at 0.5, 1.5, and 4.5 mg/kg orally daily for 4 weeks. Serum levels of nitric oxide and prostacyclin, and gene expression of endothelial nitric oxide synthase in the aortic and intrarenal tissue, were increased, whereas the serum levels of endothelin-1 and gene expression of endothelin-1 in aortic and intrarenal tissue were decreased. However, serum levels of angiotensin II and renin remained unchanged in the hyperuricemic rats treated with iptakalim. In cultured rat aortic endothelial cells, amelioration of endothelial dysfunction by iptakalim was suggested by inhibition of the overexpression of intercellular adhesive molecule-1, vascular cell adhesive molecule-1, and monocyte chemoattractant protein-1 mRNA induced by uric acid, and reversal of the inhibitory effects of uric acid on nitric oxide release in a concentration-dependent manner, which could be abolished by pretreatment with glibenclamide, an ATP-sensitive potassium channel blocker. Iptakalim ameliorated hyperuricemia in this rat model by decreasing renal damage through its antihypertensive and endothelial protective properties, and it had no direct effects on anabolism, catabolism and excretion of uric acid.

CONCLUSION: These findings suggest that the activation of ATP-sensitive potassium channels by iptakalim can protect endothelial function against hypertension and renal injury induced by hyperuricemia. Iptakalim is suitable for use in hypertensive individuals with hyperuricemia.

THANK YOU


أغرب شعر
ألوم صديقي و هذا محال
صديقي أحبّه كلام يقال
و هذا كلام بليغ الجمال
محال يقال الجمال خيال
الغريب في هذه الأبيات
أنّك تستطيع قراءتها أفقيًا و عموديًا